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(54) Title: GEL-FORMING COMPOSITIONS

(57) Abstract: Disclosed are aqueous gel-forming compositions containing a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative; an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms; an effective amount of a therapeutic or diagnostic agent; and optionally, a biocompatible inorganic salt. The gel-forming compositions exhibit an increase in viscosity upon application of shear (i.e., shear-thickening) sufficient to form a gel. The resulting gel typically relaxes over time returning to a low viscosity composition in the absence of shear. The disclosed gel-forming compositions are useful for administering a therapeutic or diagnostic agent to a patient in need of treatment or diagnosis; and for biomedical interventional procedures, such as catheter-based vascular embolization, angiogenesis, or other tissue specific applications.

GEL-FORMING COMPOSITIONS

RELATED APPLICATION

This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 60/157,365, filed October 1, 1999, the entire content of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to aqueous gel-forming compositions useful for controlled release of therapeutic or diagnostic agents and for other biomedical applications, such as catheter-based vascular embolization, angiogenesis, or other tissue specific applications. This invention also relates to methods of using such aqueous gel-forming compositions for therapeutic or diagnostic purposes.

State of the Art

In recent years, a wide variety of gel compositions have been developed for therapeutic and diagnostic purposes, such as drug delivery, medical imaging, vascular embolization and the like. For example, various polymer networks that swell and retain water (i.e., hydrogels) have been used for controlled release drug delivery and other biomedical applications. See, for example, "Hydrogels in Medicine and Pharmacy", N. A. Peppas and B. D.Barr-Howell (eds), Vol. 1 and 2, CRC Press, Boca Raton, Fla. (1986).

Hydrogels are typically prepared by cross-linking various monomers and/or polymers to provide a three-dimensional polymer network. However, many of the

monomers, polymers and cross-linking agents used in this process are not biocompatible (e.g., divinyl sulfone (DVS), glutaraldehyde, divinyl benzene, N-N-methylene-bisacrylamide, and the like). Since the cross-linking process is often incomplete, the resulting hydrogel often contains significant amounts of these non-biocompatible materials. In addition, many hydrogels are prepared using organic solvents which are not biocompatible. Accordingly, these potential sources of toxicity have limited the biomedical uses of such gels.

Other gel compositions and related materials have also been reported for use in biomedical applications. Such compositions include, by way of illustration, thermally-gelling compositions containing, for example, polyoxyethylene-polypropylene block copolymers (see, e.g., U.S. Patent No. 4,188,373); ionic polysaccharides, such as chitosan or sodium alginate; polymeric microspheres (see, e.g., U.S. Patent Nos. 5,922,357 and 5,912,017; and the like.

However, in addition to having biocompatibility problems, many of these existing gel compositions have other deficiencies or disadvantages which limit their use in biomedical applications. These deficiencies include, by way of example, complex viscosity profiles with changing temperature; decreased stability at all but a narrow pH range; high solute concentrations; instability in the presence of divalent cations; optimal formulations at low salinity ranges (i.e., at non-physiologic ranges); decreased viscosity under shear conditions and the like. Accordingly, a need exists for improved gel compositions suitable for use in biomedical applications.

In this regard, U.S. Patent Nos. 5,076,361; 5,100,567 and 5,169,559 (the disclosures of which are incorporated herein by reference in their entirety) describe shear-thickening solutions containing, for example, hydroxypropyl cellulose and sodium dodecyl sulfate or certain alkylbenzene sulfonates. These

compositions are fluid in the absence of shear. However, under shear conditions, the compositions exhibit an increase in viscosity sufficient to form a gel. Due to their shear-thickening properties, such compositions are reported to be useful for enhancing oil recovery when injected into oil fields. However, some of the disclosed compositions, i.e., those containing alkylbenzene sulfonates, are not biocompatible.

It has now been discovered that certain aqueous shear-thickening compositions comprising a hydroxyalkyl or carboxyalkyl polysaccharide derivative and an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms are biocompatible and have properties particularly useful for biomedical applications, including delivery of therapeutic or diagnostic agents to a patient, biomedical interventional procedures and the like. When used in such applications, these gel-forming compositions provide surprising and unexpected advantages compared to gels currently used for biomedical purposes.

SUMMARY OF THE INVENTION

This invention provides aqueous gel-forming compositions useful for therapeutic or diagnostic purposes. Among other properties, the gel-forming compositions of this invention exhibit an increase in viscosity upon application of shear (i.e., shear-thickening) sufficient to form a gel. In the absence of shear, the gel typically relaxes over time returning to a low viscosity composition. Therefore, the gel-forming compositions of this invention are particularly effective for the controlled release of therapeutic or diagnostic agents to a patient in need of treatment or diagnosis; and for biomedical interventional procedures requiring a transient gel composition.

Additionally, the gel-forming compositions of this invention are particularly advantageous for *in vivo* biomedical applications because the

compositions are biocompatible and may be prepared having a physiologically acceptable pH and osmotic pressure (i.e., normotonic or isotonic). If desired, the compositions can also be provided in a sterile or aseptic condition.

Accordingly, in one of its composition aspects, the present invention provides an aqueous gel-forming composition, comprising:

(a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms;

(c) an effective amount of a therapeutic or diagnostic agent; and

(d) optionally, a biocompatible inorganic salt;

wherein each of the components are present in amounts sufficient to form a gel and said composition forms a gel upon application of shear.

Preferably, the gel-forming composition forms a gel having a viscosity of at least 35,000 cP upon application of shear; more preferably, the composition forms a gel having a viscosity ranging from about 50,000 to about 3,000,000 cP upon application of shear. Preferably, the viscosity of the gel decreases over time in the absence of shear.

The gel-forming composition preferably has a physiologically acceptable osmotic pressure and pH. Preferably, the gel-forming composition is sterile or aseptic.

The hydroxyalkyl or carboxyalkyl polysaccharide derivative employed in this invention is preferably a hydroxyalkyl or carboxyalkyl derivative of alginic acid, amylose, cellulose, chitin, chitosan, dextrin, gum guar, gum xanthan and the like; or a biocompatible salt thereof. More preferably, the hydroxyalkyl or

carboxyalkyl polysaccharide is a hydroxyalkyl or carboxyalkyl derivative of cellulose. Still more preferably, the hydroxyalkyl or carboxyalkyl polysaccharide derivative is a hydroxypropyl cellulose or a carboxymethyl cellulose. Hydroxypropyl cellulose derivatives are particularly preferred.

Preferably, the hydroxyalkyl or carboxyalkyl polysaccaride derivative has a number average molecular weight ranging from about 450,000 to about 1,300,000; more preferably, from about 650,000 to about 1,150,000.

The hydroxyalkyl or carboxyalkyl polysaccharide derivative preferably comprising from about 0.39 to about 2.8 weight percent; more preferably, from about 0.5 to about 1.5 weight percent of the gel-forming composition based on the total weight of the composition.

Preferably, the alkali metal alkyl sulfate employed in the gel-forming compositions of this invention is a alkali metal dodecyl sulfate; more preferably, sodium dodecyl sulfate.

The alkali metal alkyl sulfate preferably comprising from about 0.048 to about 2.0 weight percent; more preferably from about 0.048 to about 1.5 weight percent; still more preferably from about 0.048 to about 1.0 weight percent; and most preferably, from about 0.2 to about 0.75 weight percent of the gel-forming composition based on the total weight of the composition.

In one preferred embodiment of this invention, the gel-forming composition comprises an effective amount of a therapeutic agent. Any therapeutic agent compatible with the other components of the composition may be employed in this embodiment. A preferred group of therapeutic agents for use in this invention includes vascular endothelial growth factor, fibroblast growth factor, insulin-like

growth factor, insulin, transforming growth factor, angiostatin, endostatin, prednisones, heprin, warfarin, tissue plasminogen activator and the like. Another preferred group includes chemotherapeutic agents used to treat, for example, proliferative disorders, such as cancers.

In another preferred embodiment of this invention, the gel-forming composition comprises an effective amount of a diagnostic agent. Any diagnostic agent compatible with the other components of the composition may be employed in this embodiment. Preferred diagnostic agents include gadolinium complexes, microbubbles, ionic and nonionic contrast media, biologically-targeted contrast media and the like.

Optionally, the gel-forming compositions of this invention further comprise one or more biocompatible inorganic salts. Among other properties, the biocompatible inorganic salt is used, when necessary, to provide the composition with a sufficient osmolality to form a gel and to provide the gel with a physiologically acceptable osmotic pressure and/or pH. Preferably, the biocompatible inorganic salt is sodium chloride. When present, the biocompatible inorganic salt preferably comprises from about 0.18 to about 1.0 weight percent; more preferably, from about 0.78 to about 0.94 weight percent of the composition based on the total weight of the composition. In a particularly preferred embodiment, a sufficient amount of sodium chloride is employed in the gel-forming composition to provide the composition with a physiologically acceptable osmotic pressure. More preferably, the composition is normotonic or isotonic.

If desired, the properties of the gel-forming compositions of this invention may be readily modified or optimized for a particular use by including one or more modifying agents in the composition.

In a preferred embodiment, the gel-forming composition further comprises one or more biocompatible surfactants. Among other properties, gel-forming compositions containing a biocompatible surfactant have been found to require lower amounts of alkali metal alkyl sulfate in order to form a gel under shear conditions. Preferably, the biocompatible surfactant is an alkali metal alkyl poly(oxyalkylene) sulfate. More preferably, the surfactant is a sodium lauryl poly(oxyethylene) sulfate.

In another preferred embodiment, the gel-forming composition further comprises one or more polyalkylene glycols. Gel-forming composition containing a polyalkylene glycol have been found to form gels having increased stability in the presence of lipids. Additionally, compositions containing a polyalkylene glycol require lower amounts of alkali metal alkyl sulfate in order to form a gel under shear conditions. Preferably, the polyalkylene glycol is a poly(ethylene glycol).

In yet another preferred embodiment, the gel-forming composition further comprises one or more lipids and/or phospholipids. Gel-forming compositions containing lipids and/or phospholipids have also been found to form gels having increased stability in the presence of exogenous lipids. Preferred lipids and phospholipids are selected from the group consisting of lysophosphatidylcholine, phosphatidylcholine (lecithin) and the like.

In still another preferred embodiment, the gel-forming composition further comprises one or more cross-linkable polymers. Among other properties, gel-forming compositions containing a cross-linkable polymer have been found to form gels under shear conditions and cross-linking conditions which have a stabilized three-dimensional shape. Preferred cross-linkable polymers include polyalkylene glycol diacrylates, polyalkylene glycol dimethacrylates and the like. Preferably,

the cross-linkable polymer is employed in an amount ranging from about 0.05 to about 2.5 weight percent; more preferably, from about 0.1 to about 2.0 weight percent based on the total weight percent of the composition. In this embodiment, the gel-forming composition preferably also comprises a polymerization initiator; preferably, a photoinitiator.

In yet another preferred embodiment of this invention, the therapeutic or diagnostic agent employed in the gel-forming composition is preferably encapsulated within a biocompatible polymer microsphere.

In another of its preferred composition aspects, this invention is directed to an aqueous gel-forming composition, comprising:

(a) from about 0.4 to about 1.5 weight percent based on the total weight of the composition of a hydroxypropyl cellulose having a weight average molecular weight ranging from about 650,000 to about 1,150,000;

(b) from about 0.05 to about 1.0 weight percent based on the total weight of the composition of an alkali metal dodecyl sufate;

(c) an effective amount of a therapeutic or diagnostic agent; and

(d) the remainder of the composition being aqueous saline;

wherein said composition has a physiologically acceptable pH and osmotic pressure and said composition forms a gel upon application of shear.

Preferably, this composition further comprises:

(e) from about 0.05 to about 1.4 weight percent based on the total weight of the composition of a poly(ethylene glycol).

Preferably, the gel-forming composition has an osmotic pressure ranging from about 60 mOsm/kg to about 320 mOsm/kg; more preferably from about 250

mOsm/kg to about 300 mOsm/kg; and more preferably, from about 280 mOsm/kg to about 295 mOsm/kg.

The pH of the gel-forming composition preferably ranges from about 2 to about 11; more preferably, from about 5 to about 8.

Typically, the gel-forming compositions of this invention contain a therapeutic or diagnostic agent. For some biomedical applications, however, gel-forming compositions not containing a therapeutic agent or diagnostic agent may be desirable. Accordingly, in another of its composition aspects, this invention provides an aqueous gel-forming composition, comprising:

(a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms; and

(c) optionally, a biocompatible inorganic salt;

wherein each of the components are present in amounts sufficient to form a gel and said composition forms a gel upon application of shear; and further wherein the gel-forming composition is sterile or aseptic.

The gel-forming compositions of this invention are particularly useful for delivering or administering one or more therapeutic or diagnostic agents to a patient in need of treatment or diagnosis. Accordingly, in one its method aspects, the present invention is directed to a method for administering a therapeutic or diagnostic agent to a patient, the method comprising administering to a patient in need of treatment or diagnosis a gel-forming composition comprising:

(a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms;

(c) an effective amount of a therapeutic or diagnostic agent; and

(d) optionally, a biocompatible inorganic salt;

wherein each of the components are present in amounts sufficient to form a gel and said composition forms a gel upon application of shear.

In another of its method aspects, the present invention provides a method for localized internal delivery of a therapeutic or diagnostic agent to a patient in need of treatment or diagnosis, the method comprising:

(1) selecting an internal locus for treatment or diagnosis;

(2) providing a gel-forming composition comprising (a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative; (b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms; (c) an effective amount of a therapeutic or diagnostic agent; and (d) optionally, a biocompatible inorganic salt; wherein each of the components are present in amounts sufficient to form a gel and said composition forms a gel upon application of shear.

(3) delivering the gel-forming composition to the internal locus under shear conditions to form a gel at or adjacent to the internal locus.

Preferably, the gel-forming composition is delivered by catheter, needle or aerosol.

The gel-forming composition of this invention are also useful for therapeutic interventional procedures. Accordingly, in another of its method aspects, the present invention is directed to a method for embolizing a blood vessel, the method comprising delivering into a blood vessel a sufficient amount of a gel-forming composition comprising:

(a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms;

(c) an effective amount of a therapeutic or diagnostic agent; and

(d) optionally, a biocompatible inorganic salt;

wherein each of the components are present in amounts sufficient to form a gel and said composition is delivered under shear conditions to form a gel which embolizes the blood vessel.

In yet another aspect, the present invention provides a kit for use in administering a therapeutic or diagnostic agent to a patient, the kit comprising:

(A) a first aqueous composition comprising (a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(B) a second aqueous composition comprising (b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms; (c) an effective amount of a therapeutic or diagnostic agent; and (d) optionally, a biocompatible inorganic salt;

wherein, when the first and second aqueous compositions are mixed to form a third aqueous composition, each of components are present in the third aqueous composition in amounts sufficient to form a gel and said third aqueous composition forms a gel upon application of shear.

Such kits may further comprise a delivery means suitable for a particular clinical application, such as catheters, needles/introducers, aerosols or sprays and the like.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1

Figure 1A shows the cross section of an artery treated with a composition containing a high concentration of gel-forming substance (see Example 3). The composition was delivered circumferentially. Figure 1B shows the cross section of an artery treated in the same manner with saline only as a control experiment. The morphology of the gel-treated artery appeared normal as compared to the saline control.

DETAILED DESCRIPTION OF THE INVENTION

Among other factors, this invention is based on the discovery that gel-forming compositions comprising a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative; an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms; an effective amount of a therapeutic or diagnostic agent; and optionally, a biocompatible inorganic salt are particularly useful for biomedical applications. When describing the gel-forming compositions and methods of this invention, the following terms have the following meanings unless otherwise indicated.

Definitions

"Alkali metal alkyl sulfate" refers to a compound of the formula R^a-OSO_3M, where R^a is an alkyl group and M is an alkali metal cation, such as lithium, sodium or potassium. Examples of alkali metal alkyl sulfates include, by way of illustration, alkali metal decyl sulfates, alkali metal dodecyl sulfates, alkali metal tetradecyl sulfates, alkali metal tridecyl sulfates, alkali metal undecyl sulfates and the like.

"Alkyl" refers to a monovalent saturated branched or unbranched hydrocarbon group. Examples of alkyl groups include, by way of illustration, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-hexyl, *n*-octyl,

decyl, undecyl, dodecyl, tridecyl, tetradecyl and the like. "Lower alkyl" refers to alkyl groups having from 1 to about 6 carbon atoms.

"Alkylene" refers to a divalent saturated branched or unbranched hydrocarbon group. Examples of alkylene groups include, by way of illustration, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene isomers ($-CH_2CH_2CH_2-$ and $-CH_2CH(CH_3)-$), butylene isomers, and the like. "Lower alkylene" refers to alkylene groups having from 1 to about 6 carbon atoms.

"Biocompatible" means that a component or composition is acceptable for administration to a patient or mammalian subject, i.e., is substantially non-toxic in the amount used.

"Biocompatible inorganic salt" refers to an inorganic salt acceptable for administration to a patient or mammalian subject, i.e., substantially non-toxic in the amounts used, and which comprises an inorganic cation and an inorganic anion. Examples of pharmaceutically-acceptable inorganic salts include, by way of illustration, sodium chloride, sodium bicarbonate, sodium carbonate, sodium phosphate, calcium chloride, magnesium chloride and the like, or mixtures thereof.

"Carboxyalkyl" refers to a group of the formula $-R^b-C(O)OH$ or a salt thereof, where R^b is an alkylene group of from 1 to about 6 carbon atoms. Preferred carboxyalkyl groups have the formula $-(CH_2)_mC(O)OH$, where *m* is an integer from 1 to 6, preferably 1 or 2; or salts thereof.

"Carboxyalkyl polysaccharide derivative" refers to a polysaccharide in which an average of at least 1 and preferably 2 or more hydroxyl groups per saccharide unit are substituted with a carboxyalkyl group. Examples of carboxyalkyl

polysaccharide derivatives include, by way of illustration, carboxymethyl cellulose and the like.

A "diagnostically effective amount" means the amount of a compound, agent or other diagnostic material that, when administered to a mammal to diagnose a disease or medical condition, is sufficient to effect diagnosis of the disease or condition. An "effective amount of a diagnostic agent" in the gel-forming composition means an amount sufficient to provide or to release a diagnostically effective amount of the diagnostic agent from the gel over a pre-determined period of time. The "diagnostically effective amount" may vary depending on the compound, agent or other diagnostic material, the disease and its status or severity, the age, weight, other medical conditions, etc., of the mammal to being diagnosed.

"Embolization" refers to a process wherein a material is injected into a blood vessel which thereafter fills or plugs the blood vessel and/or encourages clot formation so that blood flow through the vessel ceases. The embolization of the blood vessel is important in preventing and/or controlling bleeding (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding, bleeding associated with an aneurysm) or to ablate diseased tissue (e.g., tumors, etc.) by cutting off its blood supply. The embolizing material employed may contain diagnostic and/or therapeutic agents, such as inhibitors of angiogenesis, and the like.

"Gel" refers to a composition having a viscosity of at least 35,000 cP at 25°C; and preferably, having a viscosity in the range from about 50,000 to about 3,000,000 cP at 25°C.

"Hydroxyalkyl" refers to a group of the formula $-(R^bO)_n-H$, where R^b is an alkylene group of from 2 to about 6 carbon atoms and n is an integer from 1 to

about 5. Preferred hydroxyalkyl groups are those having the formula $-[CH_2CH(R^c)O]_n-H$, where R^c is hydrogen or lower alkyl, preferably, methyl or ethyl, and *n* is an integer from 1 to about 5.

"Hydroxyalkyl polysaccharide derivative" refers to a polysaccharide in which an average of at least 1 and preferably 2 or more hydroxyl groups per saccharide unit are substituted with a hydroxyalkyl group. Examples of hydroxyalkyl polysaccharide derivatives include, by way of illustration, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and the like. Hydroxyalkyl polysaccharide derivatives are typically prepared by reaction of the polysaccharide with an excess of an alkylene oxide, such as ethylene oxide or propylene oxide.

"Shear" refers to a shearing stress (force per unit area) applied to a liquid. Any means of producing shear in a liquid may be employed in this invention including mixing, spraying, injecting and the like.

"Tissue-specific therapy" refers to any tissue engineering application including aesthetic and tissue replacement procedures, such as breast implants, blood vessel implants, matrixes designed to be replaced by tissues of desired characteristics, such as liver, pancreas, skin, fat, vein, vascular bed, and the like.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms or signs of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but which does not yet experience or display symptoms or signs of the disease,

(2) inhibiting the disease, i.e., arresting or reducing the rate of development of the disease or its clinical symptoms or signs,

(3) relieving the disease, i.e., causing partial or complete regression of the disease or its clinical symptoms or signs,

(4) a combination of (1), (2) or (3) above encompassing different clinical symptoms or signs.

A "therapeutically effective amount" means the amount of a compound or agent that, when administered to a mammal to treat a disease, is sufficient to effect treatment of the disease. An "effective amount of a therapeutic agent" in the gel-forming composition means an amount sufficient to release a therapeutically effective amount of the therapeutic agent from the gel over a pre-determined period of time. The "therapeutically effective amount" may vary depending on the compound or agent, the disease and its status or severity, the age, weight, other medical conditions, etc., of the mammal to be treated.

The gel-forming compositions of this invention typically comprise a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative; an alkali metal alkyl sulfate; an effective amount of a therapeutic or diagnostic agent; and, optionally, a biocompatible inorganic salt. These components are further defined as follows.

Hydroxyalkyl and Carboxyalkyl Polysaccharides

Any biocompatible hydroxyalkyl or carboxyalkyl polysaccharide capable of forming a gel under shear conditions in the presence of an alkali metal alkyl sulfate and, optionally, an inorganic salt may be employed in this invention. Preferred polysaccharide derivatives include, by way of example, hydroxyalkyl and carboxyalkyl derivatives of alginic acid, amylose, cellulose, chitin, chitosan, dextrin, gum guar, gum xanthan and the like; or biocompatible salts thereof. Particularly preferred hydroxyalkyl or carboxyalkyl polysaccharide derivatives are those derived from cellulose.

Typically, the polysaccharide derivative will contain an average of at least about two hydroxyalkyl or carboxyalkyl groups per saccharide unit; and when permitted by the structure of the polysaccharide, preferably at least about 3 hydroxyalkyl or carboxyalkyl groups per saccharide unit. The hydroxyl groups or other functional groups (e.g., amino) present in each saccharide unit not substituted with a hydroalkyl or carboxyalkyl group may be present either as unsubstituted hydroxyl groups or may be substituted with other functional groups including alkyl groups, such as methyl, ethyl, propyl and the like; acyl groups, such as acetyl, benzoyl and the like; sulfonate groups ($-SO_3H$) and salts thereof; and the like.

The polysaccharide derivatives employed in this invention are either commercially available or may be prepared from commercially available starting material using known reagents and reaction conditions. For example, hydroalkyl polysaccharide derivatives are readily prepared by reaction of a polysaccharide, such as cellulose, with a molar excess of an alkylene oxide, such as propylene oxide and the like. By way of example, the preparation of hydropropyl cellulose is described in U.S. Patent Nos.3,278,520 and 3,278,521, the disclosures of which is incorporated herein by reference in their entirety.

Similarly, carboxyalkyl polysaccharide derivatives are readily prepared by the reaction of a polysaccharide, such as cellulose, with a carboxyalkyl halide, such sodium chloroacetate and the like. See, for example, Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp. 235-238.

Generally, the polysaccharide derivatives employed in this invention will have a number average molecular weight ranging from about 450,000 to about 1,300,000, preferably from about 650,000 to about 1,150,000. Typically,

polysaccharide derivatives having a lower molecular will form gels which relax more quickly compared to gels formed from higher molecular weight polysaccharides.

In a preferred embodiment, the polysaccharide derivative employed in the gel-forming compositions of this invention is a hydroxyalkyl cellulose derivative, more preferably, a hydroxypropyl cellulose. Such hydroxyalkyl cellulose derivatives preferably have an average of about 3 hydroxyalkyl groups per glucoside unit; more preferably, from about 3.4 to about 4.4 hydroxyalkyl groups per glucoside unit of the cellulose. Preferably, the number average molecular weight of the hydroxyalkyl cellulose derivative ranges from about 450,000 to about 1,300,000; more preferably, from about 650,000 to about 1,150,000. Particularly preferred hydroxyalkyl cellulose derivatives include, by way of illustration, the hydroxypropyl cellulose derivatives commercially available from Hercules Inc. (Wilmington, DE) as Aqualon HFNF HPC and Aqualon MFNF.

In another preferred embodiment, the polysaccharide derivative employed in the gel-forming composition is a carboxyalkyl cellulose derivative or a salt thereof; more preferably, a carboxymethyl cellulose or a salt thereof. Such carboxyalkyl cellulose derivatives preferably have an average of about 3 carboxyalkyl groups per glucoside unit; more preferably, from about 3.4 to about 4.4 carboxyalkyl groups per glucoside unit of the cellulose. Preferably, the number average molecular weight of the carboxyalkyl cellulose derivative ranges from about 450,000 to about 1,300,000; more preferably, from about 650,000 to about 1,150,000. Particularly preferred carboxyalkyl cellulose derivatives include, by way of illustration, carboxymethyl cellulose (commercially available from Hercules, Inc. Wilmington, DE).

Alkali Metal Alkyl Sulfates

Any alkali metal alkyl sulfate capable of forming a gel under shear conditions in the presence of a hydroxyalkyl or carboxyalkyl polysaccharide derivative and, optionally, an inorganic salt may be employed in this invention. Preferred alkali metal alkyl sulfate generally contain from about 6 to about 20 carbon atoms; more preferably, from about 10 to 14 carbon atoms; and still more preferably, about 12 carbon atoms. The optimum number of carbon atoms in the alkyl group of the alkali metal alkyl sulfate will typically depend upon the particular polysaccharide derivative employed in the gel-forming composition. For example, when a hydroxyalkyl or carboxyalkyl cellulose is employed as the polysaccharide derivative, an alkali metal alkyl sulfate having 12 carbon atoms is preferred.

Examples of preferred alkali metal alkyl sulfates include alkali metal decyl sulfates; such as sodium, potassium and lithium decyl sulfate; alkali metal dodecyl sulfates, such as sodium, potassium and lithium dodecyl sulfate; alkali metal tetradecyl sulfates, such as sodium, potassium and lithium tetradecyl sulfate; alkali metal tridecyl sulfates, such as sodium, potassium and lithium tridecyl sulfate; alkali metal undecyl sulfates, such as sodium, potassium and lithium undecyl sulfate; and the like. Particularly preferred alkali metal alkyl sulfates are sodium, potassium and lithium dodecyl sulfate, especially sodium dodecyl sulfate.

The alkali metal alkyl sulfates employed in this invention are either commercially available or may be prepared from commercially available starting material using known reagents and reaction conditions. For example, sodium dodecyl sulfate (sodium lauryl sulfate) is a commercially available anionic surfactant produced by the sulfation of dodecyl alcohol, followed by neutralization with sodium carbonate. Sodium dodecyl sulfate and related sulfates may be purchased, for example, from Sigma (St. Louis, MO) or Aldrich Chemical Co. (Milwaukee, WI).

Therapeutic or Diagnostic Agents

The gel-forming compositions of this invention are useful for administering or delivering one or more therapeutic agents, diagnostic agents or combinations thereof to a patient in need treatment or diagnosis. In this regard, any therapeutic agent or diagnostic agent compatible with the other components of the gel-forming composition may be used in this invention. Since the rate of gel relaxation in the absence of shear varies depending on the particular components employed in the gel-forming composition and the amount of each component used, the gel-forming compositions of this invention are particularly useful for the controlled release of therapeutic or diagnostic agents to a patient, including the controlled release of such materials at or adjacent to a specific site of the patient's body requiring therapeutic or diagnostic treatment.

When a therapeutic agent is employed in the gel-forming compositions of this invention, the therapeutic agent is generally present in the composition in an amount sufficient to release a therapeutically effective amount of the material over a pre-determined time period. The actual amount of the therapeutic agent administered is typically determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual therapeutic agent administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Typically, the therapeutic agent will be present in the gel-forming composition in an amount ranging from about 10^{-15} to about 50 weight percent; preferably from about 10^{-12} to about 1.0 weight percent; and more preferably, from about 10^{-9} to about 0.1 weight percent based on the total weight of the composition.

Examples of therapeutic agents suitable for use in the gel-forming compositions of this invention include, but are not limited to, the following:

analgesic agents, such as acetominophen, aspirin, ibuprofen, morphine and derivatives thereof, and the like;

anesthetic agents, such as lidocaine, novacaine, and the like;

anti-asthamatic agents, such as azelastine, ketotifen, traxanox, and the like;

antibiotics, such as neomycin, streptomycin, chloramphenicol, cephalosporin, ampicillin, penicillin, tetracycline, and the like;

antidepressant agents, such as nefopam, oxypertine, imipramine, trazadone, and the like;

anti-diabetic agents, such as biguanidines, sulfonylurea derivatives, and the like;

antiemetics and antipsychotics, such as chloropromazine, fluphenazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, triflupromazine, haloperidol, scopolamine, diphenidol, trimethobenzamide, and the like;

antifungal agents, such as amphotericin B, nystatin, candicidin, and the like;

antihypertensive agents, such as propanolol, propafenone, oxyprenolol, nifedipine, reserpine, and the like;

anti-impotence agents, such as nitric oxide donors and the like;

anti-inflammatory agents including steroidal anti-inflammatory agents, such as cortisone, hydrocortisone, dexamethasone, prednisolone, prednisone, fluazacort, and the like; and non-steroidal anti-inflammatory agents, such as indomethacin, ibuprofen, ramifenizone, piroxicam, and the like;

antineoplastic agents, such as adriamycin, cyclophosphamide, actinomycin, bleomycin, duanorubicin, doxorubicin, epirubicin, mitomycin, rapamycin, methotrexate, fluorouracil, carboplatin, carmustine (BCNU), cisplatin, etoposide, interferons, phenesterine, taxol (as used herein, the term "taxol" is intended to include taxol analogs and prodrugs, taxanes, and other taxol-like drugs, e.g.,

Taxotere, and the like), camptothecin and derivatives thereof, vinblastine, vincristine, and the like;

anti-HIV agents (i.e., anti-proeolytics);

antiviral agents, such as amantadine, methisazone, idoxuridine, cytarabine, and the like;

anxiolytic agents, such as dantrolene, diazepam, and the like;

cyclooxygenase-2 (COX-2) inhibitors;

contraception agents, such as progestogen and the like;

fertility agents;

cells, such as mammalian cells, reptilian cells, amphibian cells, avian cells, insect cells, planktonic cells, cells from non-mammalian marine vertebrates and invertebrates, plant cells, microbial cells, protists, genetically engineered cells, and organelles, such as mitochondria;

proteins including cytokines, such as interferons and interleukins; poetins; colony-stimulating factors; growth factors, such as insulin-like growth factor (IGF), transforming growth factor (TGF), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), vascular epithelial growth factor (VEGF), epithelial cell growth factor (ECGF), basic fibroblast growth factor (bFGF), bone morphogenic protein (BMP), platelet derived growth factor (PDGF); angiogenic factors, and fragments thereof and the like;

nucleic acid molecules such as genes, cDNAs encoding proteins (e.g., IGF-1 encoding sequence, Factor VIII encoding sequence, Factor IX encoding sequence), expression vectors, antisense nucleotide sequences, other oligonucleotides, ribozymes, and the like;

carbohydrates, such as Sialyl Lewis^x and the like;

extracellular matrix elements and proteoglycans, such as collagen, hyaluronic acid, fibronectin, vitronectin, dell, osteopontin, heparan sulfate, and the like, or fragments thereof;

clot dissolving or anti-thrombotic agents, such as GPIIb/IIIa inhibitors, tissue plasminogen activators, streptokinase, urokinase, heparin, and the like;

prothrombotic agents, such as thrombin, factor V, factor VII, factor VIII, and the like;

hormones, such as insulin, growth hormone, prolactin and the like;

vaccines;

immunosuppressive agents, such as cyclosporine (CsA), azathioprine, mizorobine, FK506, prednisone, and the like;

and other therapeutically or medicinally active agents.

Other suitable therapeutic agents include natural products and plant extracts; or fat-soluble vitamins, such as vitamins A, D, E, K, and the like.

The gel-forming compositions of this invention are also useful for administering or delivering one or more diagnostic agents to a patient in need of such materials. Any diagnostic agent compatible with the other components of the gel-forming composition may be used in this invention, including diagnostic agents used to aid in the diagnosis of disease and diagnostic agents used for imaging during interventional procedures, such as embolizations, abscess drainages, magnetic resonance imaging (i.e., to identify stable and unstable plaque in blood vessels) and the like.

When a diagnostic agent is employed in the gel-forming compositions of this invention, the diagnostic agent is generally present in the composition in a diagnostically effective amount. The actual amount of the diagnostic agent used will typically depend the condition being diagnosed or the interventional procedure being employed, the particular route of administration, the actual diagnostic agent administered, and the like.

Typically, the diagnostic agent will be present in the gel-forming composition in an amount ranging from about 10^{-15} to about 50 weight percent; preferably from about 0.05 to about 20 weight percent based on the total weight of the composition. Protein-based imaging agents are preferably present in the gel-composition in an amount ranging from about 10^{-12} to about 10^{-6} weight percent based on the total weight of the composition.

Diagnostic agents suitable for use in this invention include, but are not limited to, the following:

radiopaque contrast agents (for X-ray imaging), such as inorganic and organic iodine compounds (e.g. diatrizoate), radiopaque metals and their salts (e.g. silver, gold, platinum and the like) and other radiopaque compounds (e.g. calcium salts, barium salts such as barium sulfate, tantalum and tantalum oxide); paramagnetic contrast agents (for MR imaging), such as gadolinium diethylene triaminepentaacetic acid (Gd-DTPA) and its derivatives, and other gadolinium, manganese, iron, dysprosium, copper, europium, erbium, chromium, nickel and cobalt complexes, including complexes with 1,4,7,10-tetraazacyclododecane-N,N,N',N'"-tetraacetic acid (DOTA); ethylenediaminetetraacetic acid (EDTA); 1,4,7,10-tetraazacyclododecane-N,N',N"-triacetic acid (DO3A); 1,4,7-triazacyclononane-N,N',N"-triacetic acid (NOTA); 1,4,8,11-tetraazacyclotetradecane-N,N',N",N'"-tetraacetic acid (TETA); hydroxybenzylethylene-diamine diacetic acid (HBED) and the like;

ultrasound contrast agents, such as microbubble formulations;

superparamagnetic contrast agents (for MR imaging), such as magnetites, superparamagnetic iron oxides, monocrystalline iron oxides;

CT contrast agents including iodinated and noniodinated, and ionic and nonionic CT contrast agents;

and other contrast agents (for MR imaging), such as spin-labels (e.g. nitroxyl labels) or other diagnostically effective agents.

Inorganic Salts

Optionally, the gel-forming compositions of this invention may contain one or more biocompatible inorganic salts. Among other properties, the biocompatible inorganic salt facilitates gel formation under shear conditions and, depending on the inorganic salt employed, provides the composition with a physiologically acceptable osmotic pressure and/or pH. Any biocompatible inorganic salt which facilitates the formation of the gel or stabilizes the gel once formed may be used in this invention.

Preferred biocompatible inorganic salts include, by way of illustration, inorganic chlorides, such as sodium chloride, potassium chloride and lithium chloride; inorganic carbonates, such as sodium carbonate; inorganic phosphates, such as sodium phosphate and potassium phosphate; and the like, or mixtures thereof. A particular preferred biocompatible inorganic salt is sodium chloride.

When employed, the biocompatible inorganic salt will typically be present in an amount sufficient to provide the gel-forming composition with an osmotic pressure ranging from about 60 mOsm/kg to about 320 mOsm/kg, preferably from about 250 mOsm/kg to about 300 mOsm/kg, and more preferably, from about 280 mOsm/kg to about 295 mOsm/kg. In a particularly preferred embodiment, sodium chloride is used as the biocompatible inorganic salt and the gel-forming composition has an osmotic pressure similar to that of bodily fluids, i.e., is isotonic or has a osmotic pressure of about 288 mOsm/kg.

In terms of weight percent, the biocompatible inorganic salt will typically comprise from about 0.2 to about 1.0 weight percent; preferably, from about 0.7 to about 0.95 weight percent; and more preferably, from about 0.8 to about 0.9 weight percent based on the total weight of the composition.

Modifying Agents

Various modifying agents may be employed in the gel-forming composition of this invention to modify or optimize the properties of the composition for a particular therapeutic or diagnostic application.

For example, if desired, the therapeutic or diagnostic agent employed in the gel-forming compositions of this invention may be encapsulated within a biocompatible polymer microsphere. In this embodiment, the gel-forming composition serves as a vehicle for the *in vivo* delivery of the polymer microspheres. Once *in situ*, the gelled composition containing the polymer microspheres typically relaxes thereby releasing the polymer microspheres at a controlled rate. Depending on the particular application, a biodegradable polymer microsphere may be employed to subsequently release the therapeutic or diagnostic agent to the patient. Alternatively, for some applications such as certain imaging techniques in which a fluorescent, magnetic or radio-active diagnostic agent is used, a non-biodegradable polymer microsphere may be preferred.

Any polymer microsphere capable with the other components of the gel-forming composition may be used in this embodiment of the invention. Polymer microspheres are well-known in the art. For example, suitable polymer microspheres and methods for preparing microspheres are disclosed in U.S. Patent Nos. 5,922,357; 5,912,017; 5,912,015; 5,879,713; 5,828,531; 5,565,215; 4,818,542; the disclosures of which are incorporated herein by reference in their entirety.

Preferably, the microspheres have a diameter ranging from about 0.2 to about 180 microns; more preferably, from about 10 to about 110 microns. The size to the microspheres may be selected such that once the microspheres are released from the gel, they lodge in particular regions of the body, such as

extracellular matrix, soft tissues, implanted foreign bodies or capillaries, before releasing the therapeutic or diagnostic agent. For example, microparticles having a diameter of between about 10 to about 25 microns, and preferably, 15 to 20 microns, will typically lodge in a capillary.

The polymer microsphere may be comprised of a biodegradable or a non-biodegradable polymer or copolymer. Representative polymers and copolymers include poly(caprolactone) (PCL); poly(lactic acid) (PLA); poly(lactic-co-glycolic acid) (PLGA); poly(3-hydroxybutyrate) (PHB); poly(3-hydroxybutyrate-hydroxyvalerate) (PHB-HV); poly(1,4-butylene adipate) (PBA); poly(ethylene adipate) (PEA); poly(styrene) (PS); and poly(ethylene) (PE). In a preferred embodiment, a poly(alkylene glycol) polymer is also employed in the polymeric microsphere such as poly(ethylene glycol) (PEG) or poly(propylene glycol) (PPG)

Particularly preferred polymer microspheres are comprised of poly(lactic-co-glycolic acid) (PLGA) and poly(ethylene glycol) (PEG). Such polymer microspheres and methods for their preparation are described in U.S. Patent Nos. 5,282,531 and 5,565,215; the disclosures of which are incorporated herein by reference in their entirety.

In another embodiment, the gel-forming compositions of this invention may contain one or more biocompatible surfactants (in addition to the alkali metal alkyl sulfate component). Such surfactants are generally used in the gel-forming composition to reduce the amount of alkali metal alkyl sulfate required in order to form a gel under shear conditions. In such cases, delayed gelation of the compositions may be observed, however, gelation is still triggered by shear.

Any biocompatible surfactant compatible with the other components of the gel-forming composition may be used in this embodiment. Preferred biocomcompatible surfactants include, by way of example, alkali metal poly(oxyalkylene) sulfates, such as sodium lauryl ether sulfate and the like. When used in the gel-forming compositions of this invention, the biocompatible surfactant typically comprises from about 0.05 to about 0.4 weight percent; preferably, from about 0.05 to about 0.15 weight percent of the composition based on the total weight of the composition. When so employed, the molar ratio of biocompatible surfactant to alkali metal alkyl sulfate preferably ranges from about 0.1:1 to about 1:1, more preferably from about 0.5:1 to 1:1.

Similarly, one or more polyalkylene glycols may be used to decrease the amount of alkali metal alkyl sulfate required to form a gel under shear conditions. Additionally, gels containing a polyalkylene glycol have been found to have increased stability in the presence of lipids. Accordingly, gel-forming composition containing one or more polyalkylene glycols are particularly useful when the gel will be formed or used in lipid-rich environment.

Polyalkylene glycols suitable for use in this invention preferably have a number average molecular weight ranging from about 200 to about 20,000; more preferably, from about 900 to about 8,000. Preferred polyalkylene glycols include, by way of illustration, poly(ethylene glycol) (PEG or PEO), poly(propylene glycol), and the like. Particularly preferred polyalkylene glycols are poly(ethylene glycols).

When used in the gel-forming compositions of this invention, the polyalkylene glycol typically comprises from about 0.05 to about 1.4 weight percent; preferably, from about 0.1 to about 0.75 weight percent of the composition based on the total weight of the composition. When so employed, the

molar ratio of polyalkylene glycol to alkali metal alkyl sulfate preferably ranges from about 0.1:1 to about 1:1, more preferably from about 0.5:1 to 0.7:1. In some cases, the addition of a polyalkylene glycol to the gel-forming composition may result in delayed gelation under shear conditions, especially for gel-forming compositions having a polyalkylene glycol/alkali metal alkyl sulfate ratios of about 1:1.

The gel-forming compositions of this invention may also contain one or more lipids or phospholipids. Such materials have also been found to increase the stability of gels formed or used in the presence of lipids. Representative examples of lipids and phospholipids suitable for use in this invention include, by way of illustration, lysophosphatidylcholine, phosphatidylcholine, and the like. When used in the gel-forming compositions of this invention, the lipids and/or phospholipids will typically comprises from about 0.01 to about 1.4 weight percent; preferably, from about 0.1 to about 0.75 weight percent of the composition based on the total weight of the composition.

One or more cross-linkable polymers may also be employed in the gel-forming compositions of this invention to stabilize the three-dimensional shape of the gel formed under shear conditions. In this regard, gels having a defined three-dimensional shape are often desirable for certain applications, such as a breast implant, blood vessel implant, guided angiogenesis, or other tissue-specific therapy. By using cross-linkable polymers in the gel-forming compositions of this invention, the three-dimensional shape of the gels can be stabilized for use in such applications.

Preferred cross-linkable polymers for use in this invention include, by way of example, polyalkylene glycol diacrylates, polyalkylene glycol dimethacrylates, and the like. Typically, the cross-linkable polymer will have a number average

molecular weight ranging from about 200 to about 8,000; preferably, from about 400 to about 1,000. Particularly preferred cross-linkable polymers include polyethylene glycol dimethacrylates, polyethylene glycol diacrylates, and the like.

The cross-linkable polymer(s) is typically employed in an amount sufficient to stabilize the shape of the gel but insufficient to form a gel in the absence of the other components of this invention. For example, conventional known hydrogels typically employ at least about 8 weight percent of a cross-linkable polymer; and more typically, about 20 weight percent, to form the hydrogel. In the present invention, the cross-linkable polymer typically comprises from about 0.05 to about 2.5 weight percent; preferably, from about 0.1 to about 2.0 weight percent of the gel-forming composition based on the total weight of the composition. In these amounts, the cross-linkable polymer will not form a gel in the absence of the other components of this invention.

When a cross-linkable polymer is used in the gel-forming composition, a biocompatible polymerization initiator is typically employed to cross-link the polymer. Any biocompatible polymerization initiator capable of cross-linking the cross-linkable polymer may be used, including thermal and photoinitiators. For most applications, photoinitiators are generally preferred. Suitable photoinitiators include, by way of example, ethyl eosin, 2,2-dimethoxy-2-phenyl acetophenone and other acetophone derivatives, camphorquinone, and the like. The polymerization initiator typically comprises from about 10^{-12} to about 0.05 weight percent of the gel-forming composition based on the total weight of the composition. The photopolymerization is typically conducted using conventional procedures by brief exposure of the gel-forming composition to ultraviolet or visible light for a time sufficient to cross-link the polymers.

The gel-forming compositions of this invention may also contain one or more biocompatible buffering agents. Any buffering agent or combination of buffering agents compatible with the other components of the gel-forming composition and capable of maintaining or buffering the pH of the composition at a pre-determined pH or pH range may be used in the compositions of this invention. When employed, the buffering agent(s) will preferably maintain the pH of the gel-forming composition or the gel at a physiologically acceptable pH, i.e., at a pH ranging from about 2 to about 11; more preferably, from about 5 to about 8.

Suitable buffering agents include, by way of example, alkali or alkaline earth carbonates, such as sodium carbonate; alkali or alkaline earth phosphates, such as sodium phosphate; alkali or alkaline earth bicarbonates, such as sodium bicarbonate; alkali or alkaline earth citrates, such as sodium citrate; alkali or alkaline earth borates, such as sodium borate; alkali or alkaline earth acetates, such as sodium acetate; alkali or alkaline earth succinates, such as sodium succinate; tris(hydroxymethyl)aminomethane (TRIS or TRISMA®) and its salts; and the like.

One or more biocompatible preservatives may also be employed in the compositions of this invention. Representative preservatives include, by way of illustration, sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric borate, parabens, benzyl alcohol, phenylethanol, boric acid and the like. When used, the preservative will typically be present in an amount ranging from about 10^{-15} to about 0.1 weight percent based on the total weight of the composition.

Preparation of Gel-Forming Compositions and Gels

The gel-forming compositions of this invention are typically prepared by mixing or blending the components in the substantial absence of shear. Generally, a first aqueous composition comprising the hydroxyalkyl or carboxyalkyl

polysaccharide derivative is mixed or blended with a second aqueous composition comprising the alkali metal alkyl sulfate and the diagnostic and/or therapeutic agent. When present, optional components are typically included in the second aqueous composition, although such components may be present in the first aqueous composition containing the polysaccharide derivative, if desired. The first and second aqueous compositions are generally mixed or blended for a period of time sufficient to form a substantially homogeneous composition. Typically, the components are mixed or blended for about 5 seconds to about 30 seconds at ambient temperature. In the absence of shear, the resulting gel-forming composition typically has a viscosity under about 35,000 cP.

Preferably, the aqueous compositions containing the gel components are prepared using a saline solution having the desired osmotic pressure and pH, i.e., a physiologically acceptable osmotic pressure and pH. For example, aqueous compositions of gel components may be prepared using isotonic or normotonic saline or phosphate buffered saline. If desired, the separate aqueous solutions containing gel components can be sterilized, i.e., heat sterilized, prior to mixing; or alternatively, the resulting gel-forming composition can be sterilized prior to use.

Prior to formation of the gel-forming composition, the hydroxyalkyl or carboxyalkyl polysaccharide derivative is typically mixed in an aqueous solution for a period to time sufficient to hydrate the polysaccharide derivative. The period of time necessary to hydrate the polysaccharide derivative will typically vary depending on the concentration and/or molecular weight of the polysaccharide derivative, e.g., higher concentration solutions or higher molecular weight polysaccharide derivatives generally require a longer period of time period for hydration. Typically, an aqueous solution of the polysaccharide derivative is stirred for about 8 hours to about 48 hours at a temperature ranging from about

4°C to about 37°C, preferably at ambient temperature, in order to hydrate the polysaccharide derivative. Generally, hydration is complete when the solution clears and behaves homogeneously in response to shear.

The gel-forming compositions of this invention form a gel upon application of shear. Any means of producing shear in the solution may be used to gel the compositions, such as mechanical stirring, shaking, spraying, injecting and the like. The time period necessary for the composition to form a gel upon shear conditions typically varies depending on the specific components employed, their concentration and the temperature. Typically, the gel-forming compositions of this invention form a gel upon application of shear in less than 1 second to about 10 minutes at ambient temperature. The resulting gel typically has a viscosity of at least 35,000 cP; and preferably, in the range from about 50,000 to about 3,000,000 cP. In some cases, high viscosity gels may require application of additional shear for about 5 seconds to about 30 seconds about 12 to about 48 hours, typically 24 hours, after initial formation of the gel in order to attain their highest final viscosity.

Without intending to be limited by theory, it is believed that shear causes an increase in the viscosity of the gel-forming compositions of this invention by interrupting intramolecular associations between the hydroxyalkyl or carboxyalkyl polysaccharide derivative and/or the alkali metal alkyl sulfate to form intermolecular associations, i.e., micellar bridging. These intermolecular associations significantly increase the viscosity of the composition thereby forming a gel. In the absence of shear, the composition generally begins a relaxation process eventually returning to a low viscosity liquid.

The period of time necessary for the gel to relax generally varies depending on the specific components employed, the amounts used and the temperature.

Accordingly, the relaxation time for the gel can be optimized for specific uses, such as drug delivery, embolization procedures and the like. By way of illustration, gel-forming compositions having longer relaxation times in the absence of shear can be prepared by employing hydropropyl cellulose in a range of 1.0 to 1.4 weight percent, together with sodium dodecyl sulfate in a range of 0.10 to 0.5 weight percent and polyethylene glycol (MW 8,000) in a range of 0.10 to 0.5 weight percent in a solution of sodium chloride with an osmolarity of about 288, followed by application of about 5 to about 30 seconds of vortex-type shear. Such gels generally have a complete relaxation time of about 10 years or more. Alternatively, compositions having shorter relaxation times in the absence of shear can be prepared by employing hydropropyl cellulose in a range of 0.4 to 0.5 weight percent, together with sodium dodecyl sulfate in a range of 0.05 to 0.25 weight percent and polyethylene glycol (MW 8,000) in a range of 0.05 to 0.25 weight percent in a solution of sodium chloride with an osmolarity of about 288, followed by application of about 5 to about 30 seconds of vortex-type shear. Such gels generally have a relaxation time ranging from about 5 minutes to about 3 years.

If desired, the relaxation time for a particular gel-forming composition can be determined prior to *in vivo* use by infrared (IR) spectroscopy. In this regard, it has now been discovered that a novel IR absorbance peak between 1388.5 and 1368.6 cm^{-1} arises upon gel formation. This peak, which is not present in any of the component solutions, appears under shear conditions and disappears upon gel relaxation. The area of this peak is directly related to the viscosity of the composition. Accordingly, the area of the peak can be used to monitor gel relaxation. Thus, this IR method provides a means for monitoring the viscosity of the gel and gel relaxation without exposing the gel to additional shear associated with traditional viscometer measurements.

Alternatively, the rate of relaxation of a gel can be determined *in vitro* or *in vivo* using marker release experiments. In this procedure, a gel-forming composition is prepared containing a marker compound which can be readily monitored *in vitro* or *in vivo* and the release of which correlates with the relaxation of the gel. Suitable markers include, by way of example, fluorescein isothiocyanate (FITC)-dextran and the like.

Utility

The gel-forming compositions of this invention may be used to deliver a therapeutic or diagnostic agent to a patient in need of therapy or diagnosis (i.e., drug delivery) including the controlled release and/or the targeted delivery of therapeutic or diagnostic agents; for therapeutic interventional procedures, such as embolizations and the like; for biomedical imaging procedures, such as MR visualization and the like; and for coating medical devices, such as catheters, stents, valves and the like, to improve the biocompatibility of the medical device and to allow the medical device to be visualized with imaging techniques.

When used to deliver a therapeutic or diagnostic agent to a patient, a gel-forming composition is typically formulated to contain a concentration of the therapeutic and/or diagnostic agent which will release an effective amount of the agent to the patient and the resulting composition is then administered to the patient in need of therapy or diagnosis. The actual amount of the therapeutic or diagnostic agent administered is typically determined by a physician taking into consideration the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual therapeutic or diagnostic agent administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

When administering the gel-forming composition to the patient, the composition is typically subjected to shear during administration thereby forming a gel *in situ* (i.e., at the site of administration). Any suitable means for delivering the composition to the desired site under shear conditions may be employed including, for example, through a catheter, endoscope, laparoscope, needle, spray or aerosol device, and the like. Alternatively, the gel-forming composition may be subjected to shear prior to administration and the resulting pre-formed gel administered to the patient. In any event, during the procedure of positioning the gel at the desired location, the site may be accessed by either invasive surgical techniques or by relatively non-invasive techniques, such as injection, laparoscopic procedures, percutaneous transluminal procedures and the like.

After administration of the gel to the patient, the therapeutic or diagnostic agent present in the composition is typically released from the gel at a controlled rate by relaxation of the gel and subsequent liberation of the agent, or by diffusion of the agent from the gel, or combinations thereof. When the therapeutic or diagnostic agent is encapsulated within a biocompatible polymer microsphere, relaxation of the gel releases the microspheres which are then typically eroded or biodegraded thereby releasing the active agent. If desired, the rate of release of the therapeutic or diagnostic agent can be monitored by including a marker compound in the gel, the release of which can be readily monitored and correlated to the release of the active agent.

The site of administration of the gel-forming composition is typically determined by a physician in the view of the relevant circumstances, including the condition being treated or diagnosed, the therapeutic or diagnostic agent being administered, and the like. In one embodiment, the gel-forming composition is administered at a site which provides for systemic distribution of the therapeutic or diagnostic agent as it is released from the gel. Preferred sites for systemic

delivery include, by way of illustration, subcutaneous tissue, peritoneal cavity, muscle or fat and the like. Systemic distribution is particularly useful for treating or diagnosing conditions involving or effecting multiple sites, such as systemic conditions or dysfunctions, such as atherosclerosis, genetic deficiencies (such as hemophilias), or primary and metastatic neoplasms, and the like.

For example, a gel-forming composition having a long relaxation time and containing an effective amount of Factor VII can be injected subcutaneously to provide for the controlled release of Factor VII. Uptake of the released Factor VII via lymphatics then provides for systemic recirculation of the Factor VII. In this manner, replacement levels of Factor VII can be maintained in patients with deficiencies of the enzyme. Similar strategies can be employed for other systemic disorders. Alternatively, a rapid-degrading lipid-stabilized gel composition containing a targeted gadolinium complex can be delivered to a fat pad to provide a systemic longer-term contrast agent for vascular imagining or imagining of neoplastic invasions or metastases via magnetic resonance imagining techniques.

In another embodiment, the gel-forming composition is administered at a specific site to provide for localized or targeted delivery of the therapeutic or diagnostic agent. For certain conditions, local delivery is particularly useful since the effective local concentration of the therapeutic or diagnostic agent is generally much higher than the concentration that can be achieved by systemic administration. Additionally, with local delivery, the systemic concentration of the therapeutic or diagnostic agent typically remains very low thereby reducing or eliminating any side effects of the therapeutic or diagnostic agent. Local delivery is particularly useful for treating or diagnosing site specific conditions including, by way of illustration, tissue specific therapies or implants, cancers, and certain cardiovascular and vascular conditions, such as angiogenesis, restenosis after

angioplasty, coronary bypass graft atherosclerosis, transplant vascular disease, and the like.

For example, a gel-forming composition selected to relax over a 2-4 week period can be applied intra-operatively to the site of anastamosis of a saphenous vein bypass graft for coronary bypass surgery to guide venous adaptation to arterial circulation and minimize subsequent, coronary bypass graft atherosclerosis. Additionally, via a needle or direct intra-operative application, a slow-degrading gel-forming composition can be applied after excision of a suspected neoplasm so that slow release of diagnostic agents and/or chemotherapeutic or anti-angiogenic agents can be afforded in the location of the suspected lesion.

The gel-forming compositions of this invention are also useful for biomedical interventional procedures, such as embolization, quided angiogenesis, or tissue-specific therapy, such as a breast or blood vessel implant, and the like. When so employed, the gel-forming composition typically contains an effective amount of a diagnostic agent, such as a contrast agent or imaging agent, to allow the gel to be monitored *in vivo*.

By way of example, the gel-forming compositions of this invention may be employed for vascular embolization. In many clinical situations, it is often desirable to embolize blood vessels to prevent and/or control bleeding (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding, bleeding associated with an aneurysm) or to ablate diseased tissue (e.g., tumors, etc.). Compositions used for vascular embolization should be easy to deliver (e.g., low viscosity) and should cause rapid embolization in the intended vascular site (e.g., by forming a gel). Additionally, such compositions should be sterile, relatively stable, biocompatible and radiopaque. This last property is necessary in order to monitor injection of the

embolizing composition into the vascular site and to confirm its presence after the procedure is complete. Accordingly, the gel-forming compositions of this invention are particular useful as embolizing agents.

When so employed, the gel-forming compositions of this invention preferably contain an effective amount of a contrast agent, i.e., an amount sufficient to allow the gel to be monitored and/or imaged. Any contrast agent compatible with the other components of the composition may be employed. Preferred contrast agents include, by way of illustration, gadolinium-DTPA, ionic or nonionic contrast media, and the like. Typically, the gel-forming compositions will contain about 0.05 to about 20 weight percent of the contrast agent based on the total weight of the composition.

When used to embolize a blood vessel, a suitable gel-forming composition is generally prepared as described herein and a sufficient amount of this composition is introduced into the selected blood vessel under shear conditions by conventional means (e.g., injection or catheter delivery under fluoroscopy) to form a gel which embolizes the blood vessel. The amount of embolizing composition employed will vary depending on the total volume of the vasculature to be embolized.

In another embodiment, the gel-forming composition is administered at a specific site to exert a local tissue-specific effect. Examples of tissue-specific effects include enhanced local perfusion via facilitated angiogenesis, guided nerve regeneration, guided bone regeneration, mechanical cushioning of joints, blood vessel implants, breast implants, or other aesthetic implants. For example, preformed gels can be implanted to alter a soft-tissue contour defect after the excision of a neoplasm.

The gel-forming compositions of this invention are also useful for coating medical devices or accessory products, such as catheters, stents, valves and the like, to improve the biocompatibility of the medical device or accessory and to allow the medical device or accessory to be visualized with imaging techniques. Accordingly, in this embodiment, the gel-forming composition typically contains an effective amount of a contrast agent or an imaging agent. Preferred contrast or imaging agents for this application included, by way of illustration, gadolinium-DTPA, ionic or nonionic contrast media, and the like.

When used for imaging of medical devices or accessory products, a gel-forming composition is typically prepared as described herein and the resulting composition subjected to shear to form a gel. The medical device or accessory product is then coated with the gel in an amount sufficient to allow the device or accessory to be visualized using imaging techniques, such as MR imaging, CT-imaging or other radiographic techniques.

If desired, the gel-forming compositions of this invention can be provided in the form of kits for use in the above-described clinical applications and other applications. Such kits typically contain (A) a pre-determined amount of an aqueous solution of a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative and (B) a pre-determined amount of an aqueous solution of an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms, an effective amount of a therapeutic or diagnostic agent and any optional components. In such kits, the polysaccharide derivative is provided in a separate container from the other components in order to prevent premature gelling. The various components are provided in amounts sufficient to form a gel when the components are mixed and subjected to shear conditions. Optionally, such kits may contain specific delivery means for particular clinical applications, such as catheters and the like.

The following examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

EXAMPLES

In the examples below, the following abbreviations have the following meanings. Abbreviations not defined below have their generally accepted meaning.

°C	=	degrees Celsius
cm	=	centimeter
cP	=	centipoise
g	=	gram
HPC	=	hydroxypropyl cellulose
L-cfa	=	left common femoral artery
mg	=	milligram
mL	=	milliliter
mm	=	millimeter
mOsm	=	milliosmoality
MW	=	molecular weight
PEG	=	polyethylene glycol
SDS	=	sodium dodecyl sulfate
μL	=	microliter

Example 1

Preparation of a Gel-Forming Composition

A stock solution of hydroxypropyl cellulose was prepared by adding 5.6 g of Klucel HFNF (hydroxypropyl cellulose, HPC) (Hercules, Inc.) to 200 mL of normal saline (288 mOsM) in a glass 500 mL bottle and stirring the resulting mixture at about 1-2 rotations per second with a 1.1 cm (2.75 inch) magnetic stir-bar overnight at ambient temperature. Similarly, a stock solution of polyethylene glycol (PEG) was prepared by dissolving 0.7 g of MW 8000 PEG (Sigma) in 100

mL of normal saline and stirring for 15 minutes as above prior to use in the gel-forming composition. A stock solution of sodium dodecyl sulfate (SDS; Sigma) was also prepared by dissolving 1.4 g of SDS in 200 mL of normal saline.

To 50 mL of the stock SDS solution was added 12.5 mg of fluorescein isothiocyanate and the mixture was allowed to stir as above for 10 minutes (granules remained visible until dissolved and solution attained a characteristic color). To this solution was added 50 mL of the stock PEG solution and the resulting solution was stirred for 5 minutes at room temperature. A 2 mL aliquot of this solution was then mixed with 2 mL of the stock HPC solution and the resulting solution was subjected to 15 seconds of vortex shear to form a gel. The gel composition was allowed to stand for about 12 hours prior to determining the viscosity using a viscometer. The viscosity of the gel was about 3,000,000 cP.

As will be readily apparent to those skilled in the art, the fluorescein isothiocyanate employed in the above gel-forming composition may be readily replaced by other diagnostic or therapeutic agents.

Example 2

Effects of Component Concentration, Salinity and Temperature on Gel Formation

Using procedures similar to those described in Example 1, the compositions shown in Table 1 were prepared and subjected to vortex shear to determine the effects of hydroxypropyl cellulose (HPC) and sodium dodecyl sulfate (SDS) concentration, salinity and temperature on gel formation.

Table 1

HPC[1]	SDS[2]	Salinity[3]	Temp., °C	Viscosity, cP	Comments
0.4	0.200	0	RT	3000	Gel not formed
0.4	0.250	0	RT	40	Gel not formed
0.4	0.375	0	RT	21	Gel not formed
0.4	0.500	0	RT	13	Gel not formed
0.5	0.000	0	RT	114	Gel not formed
0.5	0.100	0	RT	80	Gel not formed
0.5	0.250	0	RT	800	Gel not formed
0.5	0.375	0	RT	30	Gel not formed
0.5	0.500	0	RT	25	Gel not formed
1	0.000	0	RT	2250	Gel not formed
1	0.200	0	RT	296000	Gel formed
0.5	0.250	1250	RT	72000	Gel formed
0.5	0.250	2500	RT	112000	Gel formed
0.4	0.200	5000	RT	52000	Gel formed
0.4	0.250	5000	RT	32000	Gel not formed
0.5	0.250	5000	RT	68000	Gel formed
0.5	0.375	5000	RT	36000	Gel formed
0.4	0.200	10000	RT	24000	Gel not formed
0.4	0.250	10000	RT	52500	Gel formed
0.4	0.375	10000	RT	41	Gel not formed
0.4	0.500	10000	RT	16	Gel not formed
0.5	0.000	10000	RT	175	Gel not formed
0.5	0.100	10000	RT	80	Gel not formed
0.5	0.250	10000	RT	84000	Gel formed
0.5	0.375	10000	RT	50000	Gel formed
0.5	0.500	10000	RT	61	Gel not formed

HPC[1]	SDS[2]	Salinity[3]	Temp., °C	Viscosity, cP	Comments
0.4	0.200	15000	RT	18000	Gel not formed
0.4	0.250	15000	RT	56000	Gel formed
0.4	0.375	15000	RT	24000	Gel not formed
0.4	0.500	15000	RT	20	Gel not formed
0.5	0.000	15000	RT	170	Gel not formed
0.5	0.100	15000	RT	2500	Gel not formed
0.5	0.250	15000	RT	74000	Gel formed
0.5	0.375	15000	RT	76000	Gel formed
0.5	0.500	15000	RT	9750	Gel not formed
0.4	0.200	20000	RT	15000	Gel not formed
0.4	0.250	20000	RT	46000	Gel formed
0.4	0.375	20000	RT	36000	Gel formed
0.4	0.500	20000	RT	38	Gel not formed
0.5	0.000	20000	RT	180	Gel not formed
0.5	0.100	20000	RT	3250	Gel not formed
0.5	0.250	20000	RT	57000	Gel formed
0.5	0.375	20000	RT	80000	Gel formed
0.5	0.500	20000	RT	50000	Gel formed
0.4	0.200	25000	RT	17000	Gel not formed
0.4	0.250	25000	RT	40000	Gel formed
0.4	0.375	25000	RT	51000	Gel formed
0.4	0.500	25000	RT	42	Gel not formed
0.5	0.000	25000	RT	160	Gel not formed
0.5	0.100	25000	RT	4000	Gel not formed
0.5	0.250	25000	RT	47000	Gel formed
0.5	0.375	25000	RT	82000	Gel formed

HPC[1]	SDS[2]	Salinity[3]	Temp., °C	Viscosity, cP	Comments
0.5	0.500	25000	RT	68000	Gel formed
0.4	0.200	37500	RT	7000	Gel not formed
0.4	0.250	37500	RT	26000	Gel not formed
0.4	0.375	37500	RT	56000	Gel formed
0.4	0.500	37500	RT	240	Gel not formed
0.5	0.000	37500	RT	210	Gel not formed
0.5	0.100	37500	RT	400	Gel not formed
0.5	0.250	37500	RT	27000	Salt-out
0.5	0.375	37500	RT	77000	Gel formed
0.5	0.500	37500	RT	78000	Gel formed
0.4	0.200	50000	RT	---	Salt-out
0.4	0.250	50000	RT	16000	Salt-out
0.4	0.375	50000	RT	64000	Gel formed
0.4	0.500	50000	RT	55000	Gel formed
0.5	0.000	50000	RT	210	Salt-out
0.5	0.100	50000	RT	---	Salt-out
0.5	0.250	50000	RT	---	Salt-out
0.5	0.375	50000	RT	50000	Gel formed
0.5	0.500	50000	RT	79000	Gel formed
0.4	0.375	75000	RT	56000	Gel formed
0.4	0.500	75000	RT	80000	Gel formed
0.5	0.375	75000	RT	27200	Gel not formed
0.5	0.500	75000	RT	78000	Gel formed
0.4	0.375	100000	RT	---	Salt-out
0.4	0.500	100000	RT	28000	Gel not formed
0.5	0.375	100000	RT	---	Salt-out

HPC[1]	SDS[2]	Salinity[3]	Temp., °C	Viscosity, cP	Comments
0.5	0.500	100000	RT	38000	Gel formed
0.4	0.500	100000	RT	---	Salt-out
0.5	0.500	100000	RT	---	Salt-out
1	0.200	0	40	354000	Gel formed
0.4	0.200	5000	40	26000	Gel not formed
0.4	0.250	5000	40	16000	Gel not formed
0.5	0.250	5000	40	68000	Gel formed
0.5	0.375	5000	40	10000	Gel not formed
0.4	0.250	10000	40	46000	Gel formed
0.4	0.375	10000	40	25	Gel not formed
0.4	0.500	10000	40	7	Gel not formed
0.5	0.250	10000	40	86000	Gel formed
0.5	0.375	10000	40	20000	Gel not formed
0.5	0.500	10000	40	0.5	Gel not formed
0.4	0.250	15000	40	52000	Gel formed
0.4	0.375	15000	40	8000	Gel not formed
0.4	0.500	15000	40	---	Not run - thin
0.5	0.250	15000	40	81000	Gel formed
0.5	0.375	15000	40	68000	Gel formed
0.5	0.500	15000	40	2000	Gel not formed
0.4	0.250	20000	40	43600	Gel formed
0.4	0.375	20000	40	15200	Gel not formed
0.4	0.500	20000	40	27	Gel not formed
0.5	0.250	20000	40	60000	Gel formed
0.5	0.375	20000	40	83000	Gel formed
0.5	0.500	20000	40	26400	Gel not formed

HPC[1]	SDS[2]	Salinity[3]	Temp., °C	Viscosity, cP	Comments
0.4	0.250	25000	40	41000	Gel formed
0.4	0.375	25000	40	27500	Gel not formed
0.4	0.500	25000	40	---	Not run - thin
0.5	0.250	25000	40	46400	Gel formed
0.5	0.375	25000	40	92000	Gel formed
0.5	0.500	25000	40	30000	Gel not formed
0.4	0.250	37500	40	---	Not run- thin
0.4	0.375	37500	40	52000	Gel formed
0.4	0.500	37500	40	---	Not run - thin
0.5	0.250	37500	40	17000	Gel not formed
0.5	0.375	37500	40	98000	Gel formed
0.5	0.500	37500	40	62000	Gel formed
0.4	0.250	50000	40	---	Not run -thin
0.4	0.375	50000	40	72000	Gel formed
0.4	0.500	50000	40	6000	Gel not formed
0.5	0.250	50000	40	---	Salt-out
0.5	0.375	50000	40	72000	Gel formed
0.5	0.500	50000	40	118000	Gel formed
0.4	0.250	75000	40	---	Salt-out
0.4	0.375	75000	40	6000	Gel not formed
0.4	0.500	75000	40	84000	Gel formed
0.5	0.375	75000	40	24000	Gel not formed
0.5	0.500	75000	40	134000	Gel formed
1	0.200	0	60	158000	Gel formed
0.5	0.250	5000	55	68000	Gel formed
0.4	0.250	10000	55	24000	Gel not formed

HPC[1]	SDS[2]	Salinity[3]	Temp., °C	Viscosity, cP	Comments
0.5	0.250	10000	55	88000	Gel formed
0.4	0.250	15000	55	40000	Gel formed
0.5	0.250	15000	55	70000	Gel formed
0.5	0.375	15000	55	27000	Gel not formed
0.4	0.250	20000	55	50000	Gel formed
0.5	0.250	20000	55	78000	Gel formed
0.5	0.375	20000	55	35000	Gel formed
0.5	0.500	20000	55	75	Gel not formed
0.4	0.250	25000	55	48000	Gel formed
0.4	0.375	25000	55	3500	Gel not formed
0.5	0.250	25000	55	70000	Gel formed
0.5	0.375	25000	55	86000	Gel formed
0.5	0.500	25000	55	4000	Gel not formed
0.4	0.375	37500	55	13000	Gel not formed
0.5	0.375	37500	55	62000	Gel formed
0.5	0.500	37500	55	4000	Gel not formed
0.4	0.375	50000	55	31000	Gel not formed
0.5	0.375	50000	55	82000	Salt-out
0.5	0.500	50000	55	36000	Gel formed
0.4	0.375	75000	55	112000	Salt-out
0.4	0.500	75000	55	20000	Gel not formed
0.5	0.500	75000	55	156000	Salt-out
0.1	0.200	0	70	84000	Salt-out
0.5	0.250	5000	70	14000	Gel not formed
0.5	0.250	10000	70	10000	Gel not formed
0.4	0.250	15000	70	400	Gel not formed

HPC[1]	SDS[2]	Salinity[3]	Temp., °C	Viscosity, cP	Comments
0.5	0.250	15000	70	36000	Salt-out
0.5	0.375	15000	70	800	Gel not formed
0.4	0.250	20000	70	3000	Salt-out
0.5	0.250	20000	70	35000	Salt-out
0.5	0.375	20000	70	1600	Gel not formed
0.5	0.375	25000	70	800	Gel not formed
0.5	0.375	37500	70	3000	Salt-out
0.4	0.375	50000	70	6000	Gel not formed
0.5	0.500	50000	70	1200	Gel not formed
0.5	0.500	75000	70	14000	Salt-out

1 Weight percent hydroxypropyl cellulose.

2 Weight percent sodium dodecyl sulfate.

3 Salinity in total dissolved salts (TDS) sodium chloride (ppm).

Example 3

In Vivo Administration of Gel-Forming Composition Does Not Elicit Inflammation or Toxicity

We formulated a gel ("composition A") containing 1.4 % HPC (HFNF grade Klucel, Hercules, Inc, Hopewell, VA) with 1.0% SDS (electrophoresis grade, Fisher Biotech, Fair Lawn, NJ), and 0.4% PEG-400 monomethacrylate (polysciences, Warrington, PA) cross-linked with 300 ppm photoinitiator (HMPP, polysciences Warrington, PA). This gel was selected as one of the highest concentration, highest toxicity gel composition.

All animal experiments were performed following institutional and NIH guidelines. After preinduction anesthesia with 35 mg/kg ketamine and 4.5 mg/kg xylazine, male New Zealand White rabbits were maintained on isoflurane and vitals continuously monitored and recorded each 15 minutes. The left common femoral artery (L-cfa) of each rabbit was exposed and circumferentially isolated from adjacent structures. For three animals, a total of 1.0 cc of composition A was applied perivascularly to achieve a circumferential distribution around the L-cfa from the inferior epigastric artery to the superficial femoral artery. For additional 5 animals, only 1.0 phosphate buffered saline (pH 7.2) was applied. The wound was closed in layers and the animals recovered.

After 7 days, the animals underwent total body perfusion fixation with 2L of neutral buffered formalin (NBF). The treated arterial segments were then excised and post-fixed in 10% neutral buffered formalin for 12 hours. Resulting segments were paraffin embedded. Vessels from age-matched unmanipulated controls were also harvested for each timepoint. Serial cross-sections (4um) were obtained from the proximal face of each segment using a standard rotary microtome (Leitz 1512). Two random cross sections per vessel were obtained by a blinded observer for each processing method detailed below.

Routine methods were employed, forchloroacetate esterase staining or a combination Verhoeff elastica staining and Masson trichrome, to demonstrate inflammatory neutrophilic infiltrate and general morphology, respectively. A Diagnostic Instruments SPOT true-color digital camera was used to record noninterpolated microscopic images at high resolution. The number of neutrophilic granulocytes per cross section was counted on esterase sections, with mean and standard error (SE) determined using Statview.

Mean neutrophil infiltrate per cross section ($\pm$SE) was as follows:

Composition A	0.083 ±0.083
Saline	0.333 ±0.142

(P=0.1911, Nonsignificant by posthoc testing using Fisher PLSD in ANOVA repeated measures experiment with 95% confidence)

Representative photos were taken to demonstrate that normal arterial morphology was preserved in spite of peri-arterial gel application (compared to saline controls). Figure 1A and 1B show the cross section of an artery treated with composition A and saline, respectively. No alteration in general morphology occurred in the gel treated artery when compared to the saline control. In addition, the architecture of the extracellular matrix was also undisturbed by the gel treatment as evidenced by the distribution of collagen and elastin, suggesting that the gel did not elicit either an inflammation reaction or toxicity.

Accordingly, *in vivo* application of even high concentration gels does not result in increased local inflammation or toxicity.

Example 4

***In Vivo* Administration of Gel-Forming Composition**

This procedure demonstrates another example of implantation of a pre-formed gel in an *in vivo* model. The left common femoral artery (L-cfa) of a New Zealand White rabbit (NZW) is exposed via transverse inguinal incision. The superficial femoral artery (saphenous artery) is cannulated via distal arteriotomy. A 2 mm x 2 cm Cordis SAVVY angioplasty balloon (Cordis, Miami, FL) is introduced and advanced to the inguinal ligament. The balloon is inflated to 6 atm for a duration of 1 minute then deflated and repeated prior to withdrawal. The arteriotomy is repaired. A gelled composition prepared as described in Example 1 above is applied via syringe after prior exposure to shear and is layered

circumferentially around the treated arterial segment. The wound is then closed in layers. This procedure represents one method of surgical application of a gel composition for guided arterial remodeling post interventional/surgical injury. As described herein, such a gel can also be employed to release a therapeutic factor, such as a nitric oxide donor, to provide a therapeutic effect.

Example 5

***In Vitro* Determination of Gel Relaxation Time Using IR Spectroscopy**

Using this procedure, the relaxation time for a gel can be determined using infrared spectroscopy. The gelled compositions of this invention have been discovered to have a novel infrared spectroscopy peak between 1388.5 and 1368.6 cm^{-1}. Accordingly, an approximate relaxation time for a gel can be determining by measuring the decrease in the area of this peak over time.

Using a Perkin Elmer Model 16 PC FT-IR spectrophotometer and an attenuated total reflectance cell, the area under the curve for the peak occurring between 1388.5 and 1368.6 cm-1 is determined at time zero after shear application and at a regular interval thereafter (i.e., the same time each week) for a gel. The approximate relaxation time for the gel is then determined by plotting the decrease in area of the peak vs. time.

Example 6

***In Vitro* Determination of the Release Time of a Gel Using Marker Compound**

Using this procedure, a marker compound can be used to determine the rate of release of an agent from a gel. A gel is prepared as described in Example 1. The resulting gel (4 mL) is immersed in 4 mL of normal saline. The saline solution is withdrawn daily and replaced with fresh normal saline (4 mL) for 42 days. A 200 μL aliquot from each of the saline samples is analyzed in a

fluorescence microplate reader to determine the amount of fluorophore released each day. The rate of compound release from the gel is then determined by plotting the amount of fluorophore released vs. time.

Example 7

Determination of Lipid Stability

Using this procedure, the stability of a gel in the presence of phospholipids can be determined. A stock solution of phospholipids is prepared by dissolving 20 g of 55:45 lysophosphatidylcholine: phosphatidylcholine in 100 mL of phosphate-buffered saline (pH 7.4, Gibco) while stirring at room temperature to form an emulsion. A gel-forming composition is prepared as described in Example 1 and subjected to vortex shear. Immediately after vortexing, 1.0 mL of the phospholipid stock solution is applied to the gelled composition and the mixture is sealed in a glass container which is placed in a shaking water bath at 37°C and 60 rotations per minute overnight. The viscosity of the gel formulation is evaluated, and 1.0 mL of additional emulsion is added. This procedure is continued until gel viscosity breaks below 35,000 cP. The amount of lipid emulsion required is recorded. Similar experiments are performed with other gel formulations and with other lipid/phospholipid mixtures as a measure of lipid and phospholipid stability for these gel formulations.

Example 8

Determination of pH Stability

Using this procedure, the effects of pH on gel formation and gel stability can be determined.

Effect of pH on Gel Formation: A gel-forming composition is prepared as described in Example 1 except that the pH of each of the precursor solutions is adjusted using hydrochloric acid and citric acid. A range from 2.5 to 8.5 is

examined. The viscosity of each gel is recorded 30 minutes after gel formation and again after 24 hours using a viscometer. Accordingly, the effect of pH on gel formation and viscosity can be determined.

Effect of pH on Gel Stability: A gel is prepared as described in Example 1. To samples of this preformed gel are added 4.0 mL saline solutions having a pH range from 2.0 to 10.0. After 24 hours of incubation at 37°C, the saline is withdrawn for determination of fluorophore release (as described in Example 4) and the gel composition is evaluated in a viscometer. Using this procedure, the pH stability of a preformed gel under varying pH conditions can be determined.

From the foregoing description, various modifications and changes in the compositions and methods of this invention will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

WHAT IS CLAIMED IS:

1. An aqueous gel-forming composition, comprising:

(a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms;

(c) an effective amount of a therapeutic or diagnostic agent; and

(d) optionally, a biocompatible inorganic salt;

wherein each of the components are present in amounts sufficient to form a gel and said composition forms a gel upon application of shear.

2. The composition of Claim 1, wherein the gel-forming composition forms a gel having a viscosity of at least 35,000 cP upon application of shear.

3. The composition of Claim 2, wherein the gel-forming composition forms a gel having a viscosity ranging from about 50,000 to about 3,000,000 cP upon application of shear.

4. The composition of Claim 3, wherein the viscosity of the gel decreases over time in the absence of shear.

5. The composition of Claim 1, wherein the gel-forming composition has a physiologically acceptable osmotic pressure and pH.

6. The composition of Claim 1, wherein the gel-forming composition is sterile.

7. The composition of Claim 1, wherein the hydroxyalkyl or carboxyalkyl polysaccharide derivative is a hydroxyalkyl or carboxyalkyl cellulose derivative.

8. The composition of Claim 7, wherein the hydroxyalkyl or carboxyalkyl cellulose derivative is a hydroxypropyl cellulose or a carboxymethyl cellulose.

9. The composition of Claim 1, wherein the hydroxyalkyl or carboxyalkyl polysaccaride derivative has a number average molecular weight ranging from about 450,000 to about 1,300,000.

10. The composition of Claim 1, wherein the hydroxyalkyl or carboxyalkyl polysaccharide derivative comprising from about 0.39 to about 2.8 weight percent of the gel-forming composition based on the total weight of the composition.

11. The composition of Claim 1, wherein the alkali metal alkyl sulfate is a alkali metal dodecyl sulfate.

12. The composition of Claim 11, wherein the alkyl metal dodecyl sulfate is sodium dodecyl sulfate.

13. The composition of Claim 1, wherein the alkali metal alkyl sulfate comprising from about 0.048 to about 1.0 weight percent of the gel-forming composition based on the total weight of the composition.

14. The composition of Claim 1, wherein the gel-forming composition comprises an effective amount of a therapeutic agent selected from the group

consisting of vascular endothelial growth factor, fibroblast growth factor, insulin-like growth factor, insulin, transforming growth factor, angiostatin, endostatin, prednisones, heprin, warfarin and tissue plasminogen activator.

15. The composition of Claim 1, wherein the gel-forming composition comprises an effective amount of a chemotherapeutic agent.

16. The composition of Claim 1, wherein the gel-forming composition comprises an effective amount of a diagnostic agent selected from the group consisting of gadolinium complexes, microbubbles, ionic or nonionic contrast media and biologically-targeted contrast media.

17. The composition of Claim 1, wherein the gel-forming composition further comprises a biocompatible inorganic salt.

18. The composition of Claim 17, wherein the biocompatible inorganic salt is sodium chloride.

19. The composition of Claim 1, wherein the gel-forming composition further comprises one or more biocompatible surfactants.

20. The composition of Claim 1, wherein the gel-forming composition further comprises one or more polyalkylene glycols.

21. The composition of Claim 1, wherein the gel-forming composition further comprises one or more lipids and/or phospholipids.

22. The composition of Claim 1, wherein the gel-forming composition further comprises one or more cross-linkable polymers.

23. The composition of Claim 22, wherein the cross-linkable polymer is employed in an amount ranging from about 0.05 to about 2.5 weight percent based on the total weight percent of the composition.

24. The composition of Claim 22, wherein the cross-linkable polymer is selected from the group consisting of polyalkylene glycol diacrylates and polyalkylene glycol dimethacrylates.

25. The composition of Claim 22, wherein the gel-forming composition further comprises a polymerization initiator.

26. The composition of Claim 1, wherein the therapeutic or diagnostic agent employed in the gel-forming composition is encapsulated within a biocompatible polymer microsphere.

27. An aqueous gel-forming composition, comprising:

(a) from about 0.4 to about 1.5 weight percent based on the total weight of the composition of a hydroxypropyl cellulose having a weight average molecular weight ranging from about 650,000 to about 1,150,000;

(b) from about 0.05 to about 1.0 weight percent based on the total weight of the composition of an alkali metal dodecyl sulfate;

(c) an effective amount of a therapeutic or diagnostic agent; and

(d) the remainder of the composition being aqueous saline;

wherein said composition has a physiologically acceptable pH and osmotic pressure and said composition forms a gel upon application of shear.

28. The composition of Claim 27, wherein the composition further comprises:

(e) from about 0.05 to about 1.4 weight percent based on the total weight of the composition of a poly(ethylene glycol).

29. The composition of Claim 27, wherein the gel-forming composition has an osmotic pressure ranging from about 250 mOsm/kg to about 300 mOsm/kg.

30. The composition of Claim 27, wherein the pH of the gel-forming composition ranges from about 5 to about 8.

31. The composition of Claim 27, wherein the alkali metal dodecyl sulfate is sodium dodecyl sulfate.

32. The composition of Claim 27, wherein the gel-forming composition further comprises a alkali metal alkyl poly(oxyalkylene) sulfate.

33. The composition of Claim 27, wherein the gel-forming composition further comprises one or more lipids and/or phospholipids.

34. The composition of Claim 27, wherein the gel-forming composition further comprises a polyethylene glycol diacrylate, a polyethylene glycol dimethacrylates or a mixture thereof.

35. The composition of Claim 34, wherein the polyethylene glycol diacrylate, polyethylene glycol dimethacrylates or the mixture thereof is employed in an amount ranging from about 0.05 to about 2.5 weight percent based on the total weight percent of the composition.

36. The composition of Claim 34, wherein the gel-forming composition further comprises a polymerization photoinitiator.

37. The composition of Claim 27, wherein the therapeutic or diagnostic agent employed in the gel-forming composition is encapsulated within a biocompatible polymer microsphere.

38. An aqueous gel-forming composition, comprising:

(a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms; and

(c) optionally, a biocompatible inorganic salt;

wherein each of the components are present in amounts sufficient to form a gel and said composition forms a gel upon application of shear; and

further wherein the gel-forming composition is sterile or aseptic.

39. A method for administering a therapeutic or diagnostic agent to a patient, the method comprising administering to a patient in need of treatment or diagnosis a gel-forming composition comprising:

(a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms;

(c) an effective amount of a therapeutic or diagnostic agent; and

(d) optionally, a biocompatible inorganic salt;

wherein each of the components are present in amounts sufficient to form a gel and said composition forms a gel upon application of shear.

40. A method for localized internal delivery of a therapeutic or diagnostic agent to a patient in need of treatment or diagnosis, the method comprising:

(1) selecting an internal locus for treatment or diagnosis;

(2) providing a gel-forming composition comprising (a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative; (b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms; (c) an effective amount of a therapeutic or diagnostic agent; and (d) optionally, a biocompatible inorganic salt; wherein each of the components are present in amounts sufficient to form a gel and said composition forms a gel upon application of shear.

(3) delivering the gel-forming composition to the internal locus under shear conditions to form a gel at or adjacent to the internal locus.

41. The method of Claim 40, wherein the gel-forming composition is delivered by catheter, needle or aerosol.

42. A method for embolizing a blood vessel, the method comprising delivering into a blood vessel a sufficient amount of a gel-forming composition comprising:

(a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms;

(c) an effective amount of a therapeutic or diagnostic agent; and

(d) optionally, a biocompatible inorganic salt;

wherein each of the components are present in amounts sufficient to form a gel and said composition is delivered under shear conditions to form a gel which embolizes the blood vessel.

43. A kit for use in administering a therapeutic or diagnostic agent to a patient, the kit comprising:

(A) a first aqueous composition comprising (a) a biocompatible hydroxyalkyl or carboxyalkyl polysaccharide derivative;

(B) a second aqueous composition comprising (b) an alkali metal alkyl sulfate having from about 6 to about 20 carbon atoms; (c) an effective amount of a therapeutic or diagnostic agent; and (d) optionally, a biocompatible inorganic salt;

wherein, when the first and second aqueous compositions are mixed to form a third aqueous composition, each of components are present in the third aqueous composition in amounts sufficient to form a gel and said third aqueous composition forms a gel upon application of shear.

FIGURE 1A

FIGURE 1B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/27186

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/14
US CL :424/484

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/484; 514/44, 25; 525/301

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,858,990 A (WALSH) 12 January 1999, see entire document	1-43
A	US 5,895,801 A (LEE) 20 April 1999, see entire document	1-43
A	US 5,602,104 A (SHROOT et al) 11 February 1997, see entire document	1-43

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date		
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

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